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Formulation and *in vitro* evaluation of cefpodoxime proxetil gastro retentive microspheres

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Abstract
The objective of the present study was to develop floating microspheres of Cefpodoxime Proxetil (CP) in order to achieve an extended retention in the upper GIT, to protect the prodrug from enzymatic attack which may enhance the absorption and improve the bioavailability. The microspheres were prepared by solvent diffusion method using different ratios of Cefpodoxime proxetil, hydroxyl propyl methyl cellulose (HPMC K15M) and ethyl cellulose. The floating microspheres showed better result and it may be use full for prolong the drug release in stomach and improve the bioavailability. Floating microspheres of cefpodoxime proxetil at the higher polymer to drug ratio improved the entrapment efficiency, percentage of yield as well as buoyancy percentage. In case of lower polymer to drug ratio there was a significant increase in drug release. The important factors of floating microspheres is drug release & entrapment efficiency. *In-vitro* release of formulation F7 in pH 1.2 HCl buffer and in simulated gastric fluid (SGF) were 67.52% and 68.32% respectively which showed sustained release over a period of 12 hrs and the drug entrapment efficiency 79.42%.

Keywords: Floating microspheres, cefpodoxime proxetil, hydroxyl propyl methyl cellulose, ethyl cellulose, *in vitro* release studies, bioavailability

1. Introduction
Gastro retentive microspheres form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestine [1].

Many studies have demonstrated the validity of the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drugs and improved effects in clinical situations. The results obtained have also demonstrated that the presence of gastric contents is needed to allow the proper achievement of the buoyancy retention effect.

Among the different hydrocolloids recommended for floating formulations, cellulose ether polymers are the most popular, especially hydroxypropyl methylcellulose (HPMC). Fatty material with a bulk density lower than 1 may be added to the formulation to decrease the water intake rate and increase buoyancy. Cefpodoxime proxetil is a third generation cephalosporin prodrug which is administered orally with only 50% absolute bioavailability [2].

By formulating the drug as a sustained action dosage form, especially as a floating dosage form, its bioavailability may be improved. Because of the low bioavailability of cefpodoxime proxetil due to intestinal lumen hydrolysis may be to some extent prevented. Moreover, the absorption of the cefpodoxime proxetil in the upper GIT is high [1, 3].

Preparation of floating microspheres of cefpodoxime proxetil by the emulsion-solvent diffusion method using acrylic polymers has been reported [4]. These systems allow prolonged residence time of dosage forms in the stomach and achievement of constant plasma levels; however, it is necessary to analyze the gastrointestinal transit behavior in human to confirm the suitability of the concept as far as the final design is concerned [5].

Floating drug delivery is able to prolong the gastric retention of microspheres, and thereby possibly improve oral bioavailability of cefpodoxime proxetil. Some studies have been contented to evaluate the suitability of various excipients to achieve floating dosage forms [6, 7].

Experimental

Materials & Method

Cefpodoxime proxetil was gifted sample by Panacea biotech Mohali and hydroxy propyl methyl cellulose (HPMC K 15M) from Signet chemical corporation, and ethylcellulose (EC) by Fine Chem. Labs. Mumbai. Dichloromethane (DCM), ethanol and Tween 80 were purchased from Rankem & Jiangsu Huaxi International [8, 9].

Formulation Design

The formulation was divided into nine batches prepared with different ratio of suitably chosen polymers as depicted in the table below:

Table 1: Formulation design of microspheres.

Ingredients	Formulation Codes								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cefpodoxime proxetil (gm)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Ethyl cellulose(gm)	0.5	1	1.5	-	-	-	-	-	-
HPMC K_{15}M(gm)	-	-	-	0.5	1	1.5	-	-	-
HPMC K_{15}M +EC (gm)	-	-	-	-	-	-	0.25:0.75	0.50:0.50	0.25:1.25
Dichloromethane	10	10	10	10	10	10	10	10	10
Ethanol	10	10	10	10	10	10	10	10	10
SLS(mg)	20	20	20	20	20	20	20	20	20
Tween 80	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%	0.01%
PVA(w/v%)	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75

Preparation of Floating Microspheres

Microspheres containing Cefpodoxime proxetil as a core material were prepared by emulsion solvent diffusion method. Drug and polymer were dispersed in the solvent (dichloromethane and ethanol in ratio 1:1v/v). The slurry was slowly introduced into 200 ml of water containing (0.75% w/v) polyvinyl alcohol maintained at a constant temperature of 40°c with continuous stirring at 300 rpm using a propeller type mechanical stirrer. The solution was stirred for 2 hrs. The finely developed floating microspheres were separated by filtration washed with water & dried at room temperature in a desecrator for 24h [10, 11].

FTIR Analysis

The drug-polymer compatibility was studied by FTIR (Shimadzu IR Affinity-1) spectrophotometer. The mixture of drug and potassium bromide was ground into a fine powder using mortar pestle and then compressed into a KBr discs in a hydraulic press at a pressure of 75 Kg/cm2. Each KBr disc was scanned 45 times at a resolution of 2cm–1. The characteristic peaks were recorded [12].

Buoyancy Percentage

The microspheres (0.2 g) were spread over the surface of USP (TDT 06L) dissolution apparatus (Type II) filled with 900 ml of 1.2 pH Hcl buffer containing 0.01% of Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of microspheres were recovered, dried and weighed separately. Buoyancy percentage was calculated as the ratio of the mass of particles that remained floating and the total mass of the recovered microspheres [13].

Drug entrapment Efficiency

Microspheres (equivalent to 50 mg of the drug) were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1 N HCl, repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1 N HCl. The solution was filtered and the absorbance was measured at 263 nm against appropriate blank [14, 15].

The amount of drug entrapped in the microspheres was calculated by the following formula:

DEE = (amount of drug actually present /theoretical drug load expected) × 100

Percetange Yield of Microspheres

The yield was calculated as the weight of the microspheres recovered from each batch divided by total weight of drug & polymer used in the preparation of the particular batch [16].

$$\% \text{ percentage Yield} = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$$

In-Vitro Drug Release Study

In vitro drug release studies were carried out for all batches by using USP (TDT 06L) type I dissolution test apparatus. The sample of Microspheres equivalent to 150 mg of the pure cefpodoxime proxetil was used for the study. 5 ml sample were withdrawn, diluted suitably and analyzed for the drug content spectrophotometrically at λ_{max} 263nm using dissolution media (pH 1.2 HCl Buffer and SGF) as blank [17, 18, 19].

Surface Morphology

The morphology and surface characteristics of microspheres were studied by Scanning electron microscopy (Quanta FEI 200F). The dried microspheres were coated with gold foil (100 A°) under an argon atmosphere in a gold coating unit and micrographs were obtained at both higher and lower resolutions [20, 21].

Results and discussion

FTIR Analysis

FTIR Spectra of Cefpodoxime proxetil pure Drug

The IR absorption spectra of cefpodoxime proxetil was obtained using KBR pellet technique and obtained characteristic peaks were recorded. The IR spectra of cefpodoxime proxetil exhibited distinctive peaks at 3381.57 cm^{-1} due to NH stretching of the secondary amine, 1572.66 cm^{-1} owing to –C = O stretching of the carboxyl ion and at 745.35 cm^{-1} because of C-Cl stretching.

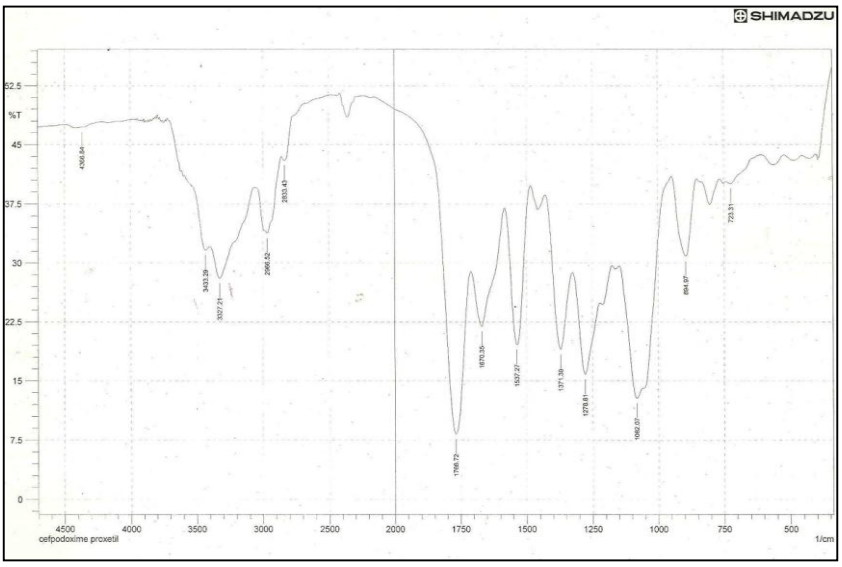

Fig 1: FTIR Spectra of Pure drug

FTIR spectra of formulation

Drug polymer compatibility was studied by obtaining FTIR spectra of different formulations and detecting the characteristic peaks. The retention of such peaks of the pure drug in formulations confirmed that it was compatible with all excipients incorporated therein.

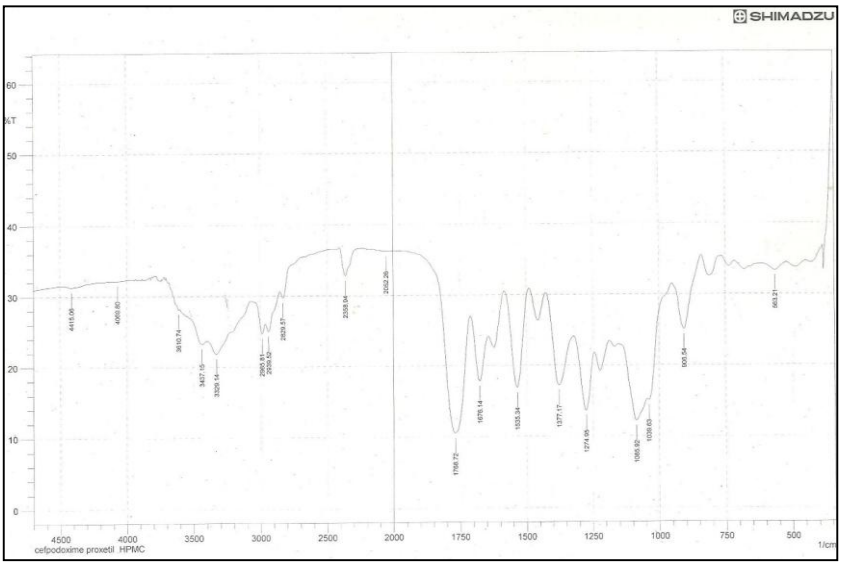

Fig 2: FTIR spectra of drug + HPMC $K_{15}M$

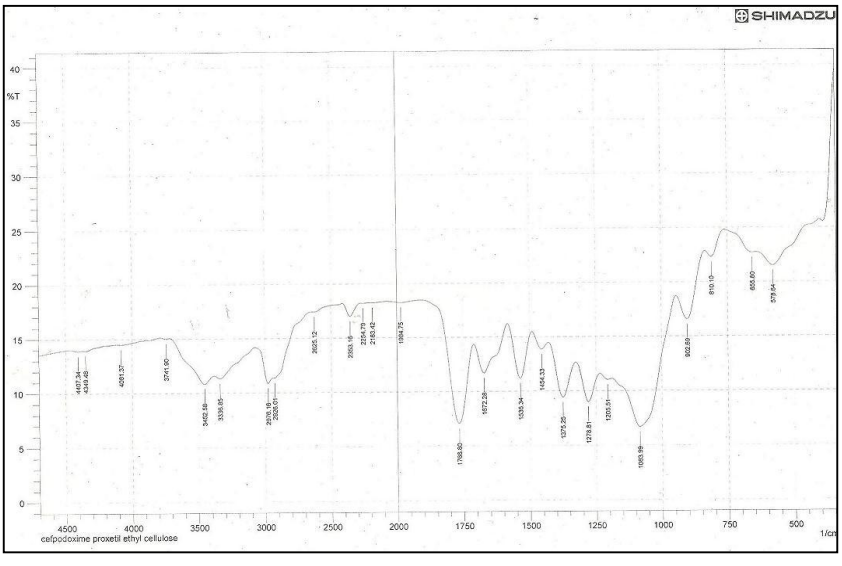

Fig 3: FTIR spectra of drug + Ethyl Cellulose

Evaluation of floating microspheres

Micromeritic Parameters

Micromeritic parameters like bulk density, tapped density, carr's index, angle of repose and hausner's ratio for formulations (F_1-F_9) were determined and found in the range of (0.25-0.69,) (0.33-0.87,) (13.46-23.56,) & (11.32-19.16) respectively.

Table 2: Results of micromeritc parameters

S.no.	Formulation Code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Angle of repose (θ)
1	F1	0.3535	0.4740	23.56	13.14
2	F2	0.2608	0.3385	21.00	19.16
3	F3	0.4602	0.5588	17.50	14.67
4	F4	0.2508	0.3376	15.28	14.34
5	F5	0.3783	0.4680	17.67	13.76
6	F6	0.3466	0.4043	14.28	14.98
7	F7	0.6923	0.8753	20.00	11.32
8	F8	0.5600	0.66400	16.67	13.34
9	F9	0.4329	0.4935	13.46	15.14

Surface Morphology

The surface morphology of microspheres was examined by scanning electron microscopy It revealed rough texture of microspheres with minute dents on the surface and exhibited different size range. The mean particle size was found to be in the range of 228.80 - 296.21 µm.

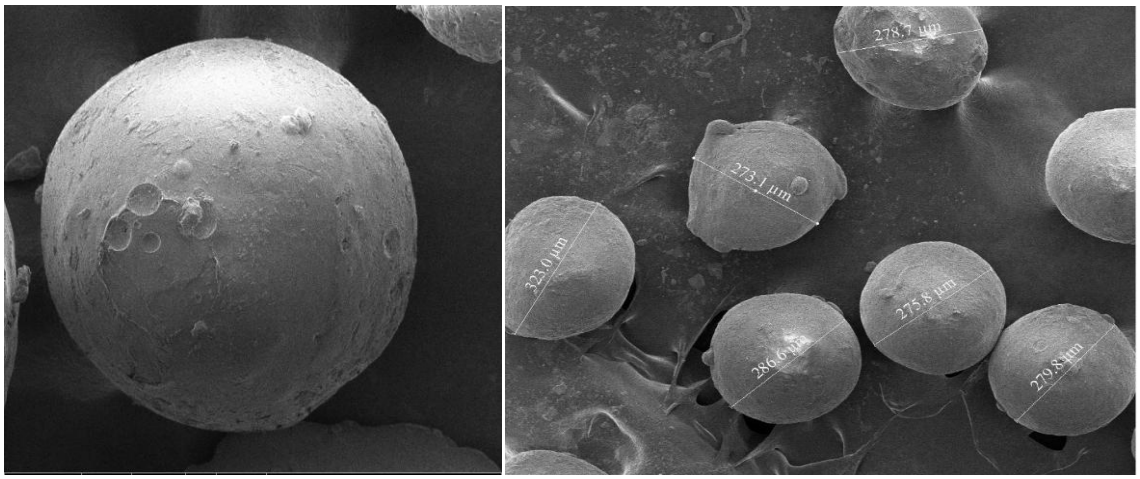

Fig 4: SEM photomicrographs of Microspherical particles

Table 3: Particle size for batch F1 - F9.

Serial no.	Formulation code	Size (µm)
1	F1	234.10
2	F2	233.44
3	F3	257.23
4	F4	239.10
5	F5	244.92
6	F6	228.80
7	F7	289.65
8	F8	296.21
9	F9	292.53

Percentage Buoyancy

The buoyancy test was carried out to investigate the floatability of the prepared microspheres. The particles were spread over the surface of a simulated gastric fluid and the fraction of microspheres settled down as a function of time was quantities. The fraction of floating microspheres reduced up to 12 hrs suggested that the absorption of the drug *in vivo* pertaining to sustained release would be linear with time.

Buoyancy of Formulations F3, F8, F9 were found to be 64.69%, 64.45% and 64.41% respectively thus indicating that microspheres were still floatable even after 12 hrs.

Drug Entrapment Efficiency

The microspheres of batch F3, F6 and F7 formulations showed entrapment of 68.77%, 76.57%, 79.42% respectively while formulations F1 and F4 particles were least entrapped. It attributed to the permeation characteristics of each polymer.

Percentage Yield

The maximum % yield was found to be 79.20% with batch F_1 and minimum of 65.92% with F_6 batch.

***In-Vitro* Dissolution Studies**

Microspheres were subjected to *in-vitro* release using USP (TDT 06L) type I dissolution apparatus. in 900 ml of simulated in pH 1.2 HCl buffer and SGF. With all the formulation there was initial intermittent burst release. But the release seems to be somewhat sustained with increased in the amount of polymer. Drug release profiles of different batches of formulations are shown in the Table No 4. The release rate was found to be decreased in accordance with the increase in ratio of polymer used. The best release was found to be with lower drug polymer ratio.

In-vitro % releases for different formulations (FA1 to FA9) were determined. It was found that the Percentage release was satisfactory. The lowest release FA2 with 57.16% release in gastric fluid and 54.70% release in pH 1.2 HCl buffer, and The highest release FA4 with 85.82% release in gastric fluid and 83.36% release in pH 1.2 HCl buffer (Figure.5).

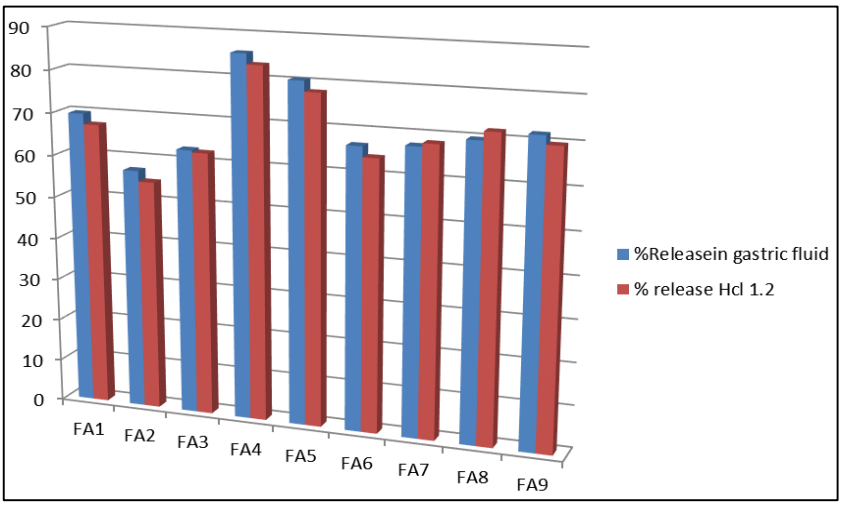

Fig 5: *In-vitro* Percentage cumulative drug release in 12h of microspheres in gastric fluid & Hcl buffer pH 1.2

The parameters which were evaluated for microspheres are given in the Table 4. Each of the six formulations containing 50 mg of the drug with various ratios of polymer (HPMC K15M/EC) from 1:1 to 1:3 was taken. No drug-polymer incompatibility was noted in their FT-IR spectra. The entrapment percentages for different formulations (FA1 to FA9) were determined. It was found that FA_7 entrapment 79.42%. In general, with formulation (FA_7), the Percentage entrapment Efficiency was satisfactory. The lowest entrapment (50.91%) was with FA_1 (Table 4).

The buoyancy percentage for all batches was almost above 50%, which was studied for 12 h. buoyancy in percentage was found to be 52.59% to 64.69%.

Table 4: Evaluation parameters of cefpodoxime proxetil floating microspheres.

Form	% Yield	% En. Efficiency	Buoyancy %	% in Gastric fluid	% in HCl buffer
FA_1	79.20	50.91	57.41	69.75	67.29
FA_2	75.80	63.60	62.60	57.16	54.70
FA_3	71.60	68.77	64.69	62.95	62.49
FA_4	74.60	54.24	53.72	85.82	83.36
FA_5	69.10	68.51	52.59	80.47	78.01
FA_6	65.92	76.57	54.57	66.71	64.25
FA 7	78.60	79.42	59.52	67.52	68.32
FA8	76.14	58.87	64.45	69.80	71.85
FA9	71.90	61.99	64.41	71.84	69.78

Conclusion

Floating microspheres of cefpodoxime proxetil were prepared using HPMC and EC, at the higher polymer to drug ratio improved the entrapment efficiency, percentage of yield as well as buoyancy percentage. In case of cefpodoxime proxetil floating microspheres, at the lower polymer to drug ratio there was a significant increase in drug release, seen at the 1:2 ratio. FA_7 formulation have 1:2 drug polymer ratio so formulation FA_7 found to be the best formulation among the various polymer to drug ratios because it is show good release with good entrapment efficiency.

The other physicochemical parameters determined with the microspheres were bulk density (0.25-0.69g/ml), particle size distribution (228.80 - 296.21µm), % yield (65.92%-79.20%), buoyancy % in pH 1.2 HCl buffer (52.59%- 64.69%) and drug entrapment efficiency (50.91%-79.42%). The *in vitro* drug release in pH 1.2 HCl buffer ranged from 83.36%-54.70% while in simulated gastric fluid it ranged from 85.82%-57.16%. The overall determinations suggested F7 batch as the best formulation.

All above data satisfactorily complied with the characteristics requirements of the formulation as gastroretentive floating microspheres. The present worker tended to provide impetus for future researchers to design such novel drug delivery systems which can supersede conventional dosage forms with significant pharmacokinetic and pharmacodynamic properties.

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